PALM INTRANET

Day : Saturday
Date: 3/18/2006
Time: 00:03:49

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Neuropathic Pain: Diagnosis, Treatment, and the Pharmacist's Role in Patient Care

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Learning Objectives

After participating in this activity, participants should be better able to:

- Review the types and prevalence of **neuropathic pain**.
- Understand the direct and indirect costs of **neuropathic pain**.
- Discuss the diagnosis of **neuropathic pain** and why this condition can be misdiagnosed.
- Review the benefits and risks associated with current treatments.
- Evaluate new and emerging treatments for **neuropathic pain**.
- Specify the role of the pharmacist in providing medication therapy management services to the patient with **neuropathic pain**.
- Provide counseling points for patients with **neuropathic pain**.
- Review resources available to the pharmacist about chronic and **neuropathic pain**.

ACPE Program I.D. Number:
290-000-05-013-H01

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Neuropathic pain afflicts an estimated 4 million people in the United States.[1] The condition originates from an injury to either the peripheral or central nervous system (CNS) or to both and develops into a chronic disorder. Examples of **neuropathic pain** syndrome include diabetic peripheral neuropathy (DPN), phantom limb **pain**, HIV sensory neuropathy, postherpetic neuralgia (PHN), central poststroke **pain**, low back and neck **pain** with a **neuropathic** origin, complex regional **pain** syndrome, and multiple sclerosis **pain**. It is estimated that of the 18 million patients with diabetes in this country, 5% to 50% are affected by DPN, with the incidence and prevalence increasing over the number of years with diabetes.[2] About 800,000 people in the United States each year develop shingles, with 25% to 50% developing PHN as a complication of the herpes zoster virus.[3] Being 50 years of age or older is a risk factor for developing PHN following herpes zoster. This painful condition severely affects the ability of the individual to perform daily activities and ultimately affects his or her overall quality of life. Central **neuropathic pain** is estimated to occur in 2% to 8% of all stroke patients.[4] **Neuropathic pain** is also associated with chemotherapy and direct traumatic injury to the nerves. Table 1 lists common underlying causes of

neuropathic pain.

Neuropathic pain is classified as a type of chronic **pain**. It **differs** from acute nociceptive **pain**, which is **pain** caused by the normal activation of neural pathways in response to a **pain**-initiating stimulus. Hallmark characteristics of **neuropathic pain** are lowering of the **pain** threshold and excitation of the nerve pathways long after the initial injury has healed. The **pain** becomes chronic in nature, and severe, and often is not responsive to the usual treatments for acute **pain**. The CNS is composed of the brain and spinal cord, whereas the peripheral nervous system includes nerves to the hands, feet, legs, and arms, and the link, at the dorsal horn, between the spinal cord and the rest of the body. **Neuropathic pain** results from damage to or changes in the central and peripheral nervous systems. The injury and malfunction to the nervous system become the source of **pain** and become a chronic disease.

Underlying Causes of Neuropathic Pain

- Alcoholism
- Diabetes
- Acquired immune deficiency syndrome/HIV
- Postherpetic neuralgia
- Trigeminal neuralgia
- Amputation resulting in phantom limb pain
- Cerebral vascular accident
- Trauma to the lower back or cervical region
- Multiple sclerosis
- Fibromyalgia
- Complex regional pain syndrome
- Chemotherapy

Table 1

An understanding of the pathophysiology of **neuropathic pain** allows the clinician to target particular neurochemicals and receptor sites with appropriate rational pharmacotherapy. The pathophysiology of **neuropathic pain** is complex and mediated through a variety of mechanisms. Beginning with injury to the nerve, sensitization and overstimulation of the nerve pathways occurs, along with release of excitatory neurochemicals and inflammatory neuropeptides. C fibers are the small unmyelinated or unsheathed afferent nerves taking impulses from the periphery to the spinal cord. They conduct nerve impulses relatively slowly, are of a low threshold nature, and penetrate deep into the spinal cord. Repetitive stimulation of the C fibers results in prolonged discharge or spontaneous activity of the neuron in the dorsal horn of the spinal cord. This sensitization leads to release of excitatory amino acids such as glutamate. Glutamate is a neurochemical that can attach itself to the *N*-methyl-D aspartate (NMDA) receptor site and further excite other neurons. It follows that agents that are NMDA-receptor antagonists, such as ketamine, dextromethorphan, and memantine, could block this excitation. Sensitization in the dorsal horn eventually leads to increased activity of neurons or hyperexcitability of the nerves and a decrease in the **pain** threshold. An increased number of adrenergic receptors can develop along the length of the C fibers, resulting in increased sensitivity and an increase in sympathetically mediated **pain** signals. Agents that prevent reuptake of catecholamines at these receptor sites, such as tricyclic antidepressants (TCAs), are effective in preventing **pain** signal transmission. Nerve injury in the periphery also can result in the release of inflammatory neuropeptides, substance P, and prostaglandins. Another mechanism of **pain** transmission is the continuous electrical discharge along the nerve fiber resulting in "ectopic" activity. These electrical discharges continue to fire, generating impulses even in the absence of stimulation or injury and are related to an increase in the number of sodium channels. Sodium channels facilitate sodium influx, enabling continuation of the action potential or electrical impulse to travel along the nerve pathway. Anticonvulsant agents are useful in blocking these channels. Ectopic discharges also occur in the cells at the dorsal root and lead to hyperactivity of the neurons in the spinal cord.

Economic, Human, and Societal Costs

Neuropathic pain is costly. Individuals affected by **neuropathic pain** are oftentimes high users of the health care system as they search for relief from persistent suffering. Much of the available cost data defines costs relative to chronic **pain** in general so that costs attributable to **neuropathic pain** are contained with those numbers. The American **Pain** Society conducted a survey demonstrating that most people with chronic/persistent **pain** had been experiencing their **pain** for more than 5 years, and one third described the **pain** as the "worst ever." Many sufferers had to visit multiple physicians to achieve only partial relief from their **pain**.[5]

Direct and indirect costs of persistent **pain**, including **neuropathic pain**, are derived from economic, human, and societal components. The economic burden relates to direct medical costs and productivity loss in the workplace. Chronic **pain** sufferers may become unemployable or remain underemployed. The National Institute for Occupational Safety and Health estimates that chronic **pain** costs $100 billion annually in lost workdays, medical expenses, and other benefit costs.[6] In terms of human costs, living with chronic **pain** affects patients' day-to-day ability to function. Physical and mental problems include difficulties in sleeping, impaired concentration, and decline in cognitive abilities. **Pain** contributes to disruption of sleep patterns, which can foster irritability, leading to enhanced sensitivity to **pain**, and the patient becomes caught up in a vicious cycle. Anger, fear, depression, and anxiety are common and may lead to suicidal ideations, attempted suicide, or successful suicide.

Neuropathic pain is also responsible for societal burdens. The patient with **neuropathic pain** becomes isolated because of the loss of functioning, and the impact on the family can strain relationships. For these reasons, patients benefit from a multidisciplinary approach to treatment. Team members such as a psychiatrist, psychologist, social worker, occupational and physical therapist, nurse, pharmacist, and physician are integral to treating the patient holistically.

Diagnosis of Neuropathic Pain: The Role of the Pharmacist

Neuropathic pain can be misdiagnosed and treated as musculoskeletal **pain**. When the diagnosis of **neuropathic pain** is overlooked, the patient may be treated inappropriately, leading to months or even years of mismanaged chronic persistent **pain** and decreased function. The pharmacist can assist in the recognition of this condition, which manifests in heterogeneous symptoms (Table 2).

Symptoms Characteristic of Neuropathic Pain
Burning
Tingling
Electric shock-like
Shooting
Radiating
Stabbing
Pins and needles

Table 2

It can be difficult for the patient to separate the **neuropathic pain** from other chronic **pain**, particularly if there is tissue damage. In addition, patients may be unfamiliar with the terminology to describe this type of **pain**, or do not think this complaint is important enough to share with the physician, adding to the difficulty in diagnosing this type of **pain**. Patients may find it difficult to describe the **pain** and complain of exaggerated responses to slightly painful stimuli. The **pain** may present months after the initial nerve injury. Common questions that pharmacists may face include, what is **neuropathic pain**, and why do I experience this type of **pain**? What is the difference between nerve and muscle **pain**, and is this type of **pain** serious? Can nerve **pain** have a variety of symptoms, and can it affect my sleep? Can nerve **pain** be cured?

When assessing the patient, various bits of information should be obtained. Pharmacists can assess patients for **pain** in a primary care/ambulatory care practice as part of the vital signs package, **pain** being the 5th vital sign, and upon follow-up to determine therapeutic effect of interventions, which are primarily pharmacologic. The pharmacist should review all the components of **pain** assessment, such as the onset/ duration of **pain**, location, quality, intensity, aggravating or relieving factors, and emotional factors contributing to or the result of **pain**. Certain key terms used to describe the **pain** are specific to **neuropathic pain**, including burning, tingling, electric shock-like, shooting, radiating, or statements such as "it feels like I am walking on broken glass." For example, diabetic neuropathy has been described as pins and needles in the feet, legs, or hands. Descriptions of constant, stabbing, and electric shock-like sensation can be representative of PHN. Other associated characteristic descriptions of **neuropathic pain** are related to the unique physiology of this type of **pain**. The patient may say that even the bed sheets hurt. Such patients may be suffering from allodynia associated with the **neuropathic pain**. Allodynia is the perception of **pain** to a greater degree than would be expected considering the **pain** stimulus. More specific diagnosis by the physician may reveal the underlying cause of the neuropathy. See Table 3 for diagnostic testing performed by the physician.

Patients suffering with chronic **pain/ neuropathic pain** usually have a long history of seeking treatment, because the relief achieved is usually only partial. Patients should be questioned as to the current and prior attempts to manage their own **pain**, and what treatment or strategy was successful and what was not. Treatment strategies include pharmacologic treatments, alternative treatments such as chiropractic and acupuncture, and coping strategies. It is useful to explore the patient's history of medical problems relative to surgeries and accidents; psychosocial history such as job stressors, unemployment, compensation issues; family history focusing on interpersonal dynamics; and psychological effects of the persistent **pain** on mental status and emotions to get a comprehensive picture of the patient. The patient's functional baseline should also be assessed as it relates to the patient's work, family activities, care for the house and other family members, and the ability to participate in sports or hobbies.

Diagnostic Testing
Neurologic assessment: cranial nerves, touch (filament test), pain (pin-prick), temperature, vibration
Muscle strength, gait patterns, coordination
X-ray
Magnetic resonance imaging
Computed axial tomography
Lumbar puncture
Encephalography
Electromyography
Laboratory analysis of blood and urine

Table 3

Neuropathic pain in the diabetic patient can be thought of as the forgotten symptom, being lost in the myriad of other higher-priority medical problems. The pharmacist can conduct baseline and periodic assessment of the patient's reported **pain** by using the visual analog scale or the numeric rating scale (NRS) along with the **neuropathic pain** scale (NPS) and by performing a filament examination of the feet. The NPS might help the clinician to identify distinct **pain** symptoms and target specific treatment depending on the quality of the **pain** reported. The scale focuses on adjectives that have been shown to be associated with **neuropathic pain**. In the NPS scale, the patient is asked to measure intensity, severity, and qualities such as sharp, hot, dull, cold, sensitive, itchy, deep **pain**, or surface **pain**.[7]

The physician will perform the neurologic examination and possibly order various diagnostic studies to assist in the assessment of the patient's **pain**. The neurologic exam begins with sensory testing for touch, **pain**, temperature, and vibration. The patient will also be assessed for **pain** perception—allodynia is assessed with a nonpainful stimulus, and hyperalgesia is assessed with pinpricks. Muscle strength, coordination, and gait pattern can be observed as an indication of limitations imposed by nerve **pain**, which can compromise the skeletal structure over time. Additional diagnostic studies such as x-ray, computed axial tomography (CAT) scan, or magnetic resonance imaging (MRI) can be ordered to rule out medical problems that could be treated, leading to a resolution of the **pain** complaint. Underlying causes of nerve **pain** include diseases such as acquired immune deficiency syndrome (AIDS), diabetes, cancer, or shingles. Peripheral neuropathy may be associated with diabetes, renal failure, chemotherapy, amyloidosis, infections such as HIV, PHN, nerve entrapment, amputation, or ischemia. Central neuropathy follows an injury to the CNS secondary to trauma, malignancy, inflammation, vascular problems, cerebrovascular accident, or multiple sclerosis.

Laboratory and serologic analysis may also be used to rule out medical problems. Electromyography and nerve conduction velocity tests have limitations in that these do not necessarily assess the specific function of the small nerve fibers and the C fibers involved in the pathophysiology of **neuropathic pain**.

The Pharmacist's Plan of Care

The pharmacist's plan of care involves a discussion of the expectations and goals of treatment. A clear understanding of the treatments ordered can be reviewed along with the schedule for monitoring therapies and laboratory follow-up. Because **neuropathic pain** takes a chronic course, it is usually only partially responsive to treatments. The **pain** more than likely will not be totally eradicated, so the patient needs to be counseled about setting realistic expectations and achievable goals. Questions to consider include "What are the functional abilities the patient hopes to

achieve, such as the ability to ambulate? What will be the overall quality of life the patient hopes to achieve?"

Patients with **neuropathic pain** frequently develop comorbidities such as insomnia, depression, and anxiety. The pharmacist assessing the patient for insomnia should ask the following questions:

- "Do you have difficulty getting to sleep or staying asleep?"
- "Do you wake up early in the morning such as by 3:30 or 4 AM?"

The pharmacist should also review sleep hygiene in general, including napping patterns during the day. All of these efforts will contribute to improved sleep patterns and decreased fatigue and drowsiness the next day, contributing to a better quality of life. Depression and anxiety can be assessed using standard self-rating scales and by checking for the presence of symptoms listed in the *Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition* (DSM-IV-R). Such symptoms include feelings of guilt or lack of self-worth, isolation from family and friends, crying spells, lack of appetite, weight loss, waking early in the morning, difficulty in concentrating, irritability, and feelings of fatigue. Symptoms of anxiety include excessive worry about events or activities where the individual cannot control these feelings, restlessness and feeling edgy, fatigue, trouble concentrating, irritability, insomnia, increased muscle tension. In depression and anxiety, the symptoms are considered severe enough to impair the patient's ability to work or impair social, family, or personal relationships.

Approaches to the Management of Neuropathic Pain

Nonpharmacologic

- Acupuncture
- Transcutaneous electrical nerve stimulation
- Psychotherapy
- Relaxation techniques
- Patient education
- Surgery

Pharmacologic

- Tricyclic antidepressants
- Anticonvulsants
- Gabapentin
- Pregabalin
- Lidocaine patch
- Opioids
- Tramadol

Table 4

Current Treatments

Treatments for **neuropathic pain** cover a wide range of options reflecting the multidisciplinary nature of care for the patient (Table 4). Treatments include psychological management of the chronic **pain** through stress management, relaxation, biofeedback, cognitive behavioral techniques, and counseling by a psychologist or psychiatrist. In addition, multiple agents are offered as pharmacologic treatment of **neuropathic pain**. Often these agents are used in combination, with continued evaluation for efficacy being a crucial element of the management process. Patients may respond poorly to any single agent or a combination of agents. Finding the effective treatment is often a challenging and labor-intensive journey.

Pharmacologic Agents

A number of pharmacologic agents are available for the treatment of **neuropathic pain** (Table 5). First-line agents include TCAs, gabapentin, topical lidocaine, opioids, and tramadol.[8] Pharmacotherapy is considered not only for **pain** management but also to treat common comorbidities such as depression and anxiety. The TCAs and antidepressants exhibiting the mixed mechanism of serotonergic and adrenergic reuptake blockade are more effective for the treatment of **neuropathic pain** than the selective serotonin reuptake inhibitors. Clinical trials of TCAs have demonstrated efficacy in DPN, although the drugs are not FDA-approved for this indication. Clinical trials have evaluated amitriptyline, clomipramine, desipramine, imipramine, and nortriptyline. In these combined clinical trials of approximately 300 people participating in the active-therapy group, approximately one third of the patients received a 50% reduction in **pain**.[8] In general, dosing may be initiated at 10 mg to 25 mg at bedtime with weekly increments of 25 mg to a target dose of 150 mg daily. Pharmacists are well aware of the side-effect profiles of TCAs, such as dry mouth, constipation, increase in appetite and weight gain, urinary retention, and somnolence. The tertiary amines, such as desipramine and nortriptyline, may be preferred over amitriptyline, because they are better tolerated by the patient. Serious risks, especially in the elderly, are cardiac conduction disturbances and

orthostatic hypotension.[9]

Pharmacologic Treatment Options

Suggested First-line Agents	Dose/Note	Suggested Second-line Agents	Dose/Note
Tricyclic antidepressants	Desipramine nortriptyline: start at 10-25 mg at bedtime, and titrate every 3 days up to 20-100 mg daily. Follow up in 1-2 weeks for therapeutic effect.	Anticonvulsants	Lamotrigine: start at 25-5(daily up to 400-600 mg in 2 divided doses daily. Divalproex: start at 250 m bedtime, and titrate to 25(500 mg 2-3 times a day. Topiramate: start at 25 mg and titrate to dose of 400 daily in divided doses. Ma up to 12 weeks for evalua
Gabapentin	Start at 300 mg at bedtime, and titrate by 300 mg every 3-7 days to a maximum of 1800-3600 mg/day in 3 divided doses. Elderly: start at 100 mg at bedtime, and titrate by 100 mg every 3-7 days. First follow-up in 2 weeks for therapeutic effect.		
Pregabalin	DPN: Dosing should begin at 50 mg 3x/day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. PHN: Dosing should begin at 75 mg 2x/day or 50 mg 3x/day and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Note: Because this drug is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function.		
Lidocaine patch	One patch daily on for 12 hours, off for 12 hours. Up to 4 patches.		
Opioids	Oxycodone: 5-10 mg q 4-6 hours if IR or 20-160 mg in 2 divided doses if ER. Methadone: start at 5 mg at bedtime up to 20-80 mg in 1-4 divided doses. CAUTION in titration schedule and evaluation.		
Tramadol	Start at 37.5-50 mg daily, and titrate up to 200-400 mg in 2-3 divided doses.		

DPN = diabetic peripheral neuropathy; PHN = postherpetic neuralgia.

Table 5

Gabapentin is FDA-approved for PHN and is used extensively off-label for diabetic neuropathy and other neuropathies. The effectiveness of gabapentin in the treatment of DPN and PHN has been demonstrated in 2 large placebo-controlled, randomized, double- blind clinical trials.[10,11] Doses used in these studies ranged from 900 to

3600 mg daily given in 3 divided doses. **Pain** relief was generally achieved early in therapy and at doses above 1800 mg per day. In another study, **pain** scores of patients with diabetic neuropathy decreased from an average of 6.5 NRS to 4.0, with effective doses ranging from 1800 to 2400 mg.[12] In addition, a review has summarized the evidence for gabapentin in treatment of PHN.[13] The reviewers found 2 randomized, placebo-controlled, parallel-group, multicenter clinical trials demonstrating the efficacy of gabapentin in PHN at doses of up to 3600 mg/day. The drug is renally excreted, so there is little to no opportunity for potential drug interactions. The common adverse effects of gabapentin are somnolence, fatigue, and lack of coordination. This necessitates slow titration of the dose to effective levels. From clinical experience, an appropriate trial to assess **pain** relief, titrate, and balance side effects will take at least 2 to 4 weeks. Even after this time period, patients most likely will have some residual **pain**.

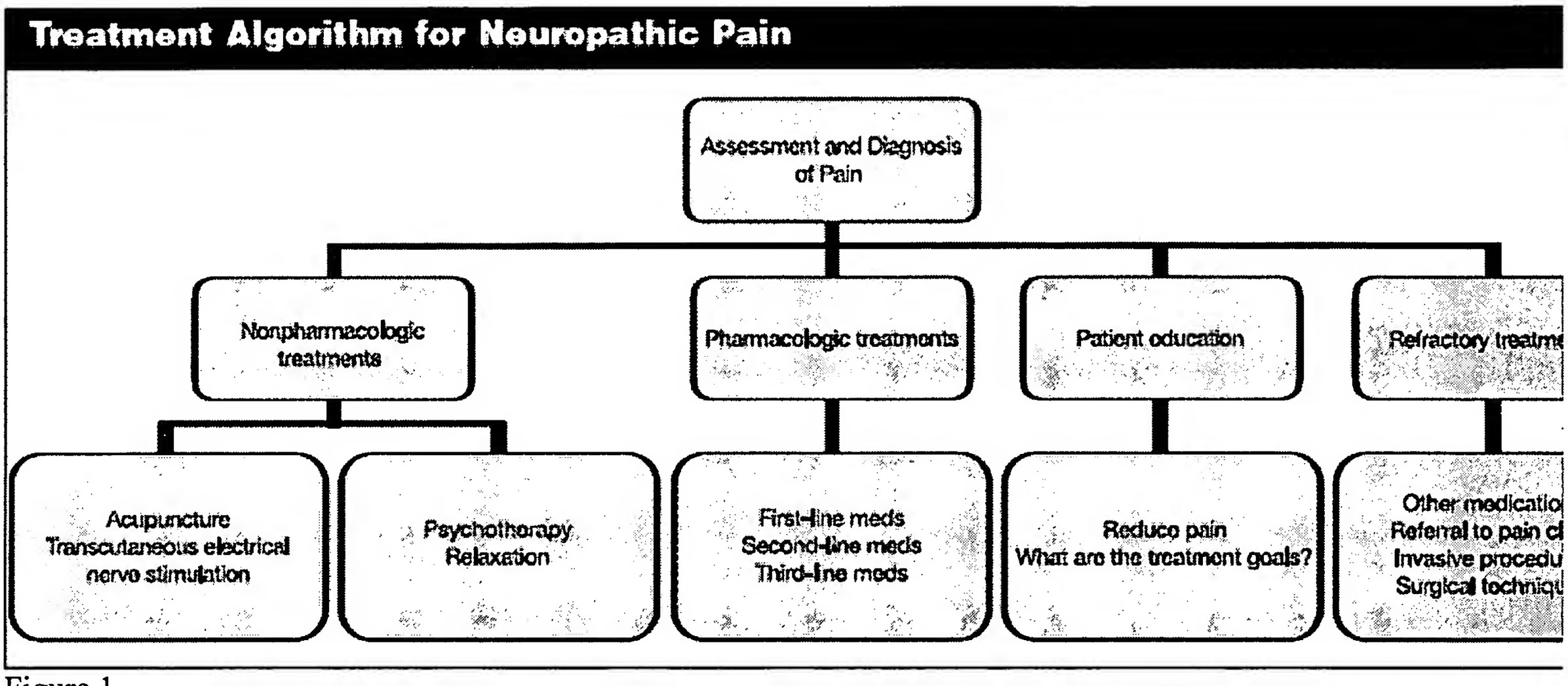

Figure 1

The topical lidocaine patch is FDA-approved for postherpetic **pain**. The patch may be applied locally to relieve **pain** for a period of 12 hours and then removed. Several randomized clinical studies have demonstrated the efficacy of the patch in the treatment of PHN.[14-16] The patch was well tolerated with only mild redness reported at the site of application.

Historically, opioids have not been a widely accepted treatment for patients with **neuropathic pain**. In the elderly, however, opioids may actually be the best choice to treat moderate-to-severe **pain** because this age group does not tolerate other agents well, and clinical trials indicate opioid efficacy in the treatment of **neuropathic pain**. One study demonstrated effective use of opioids in 81 patients with central or peripheral **neuropathic pain** using either a low- or high-dose regimen of levorphanol.[17] The investigators assessed patients for **pain** relief and quality-of-life indicators, demonstrating improvement in 1 month. The quality-of-life indicators include ability to ambulate, mood, general activity level, ability to work, quality of relationships, sleep patterns, and overall enjoyment of life.

Oxycodone has been evaluated in both PHN and DPN. In a study of 50 PHN patients receiving oxycodone, patients reported relief of steady **pain**, spontaneous **pain**, and allodynia in this randomized, double-blind, crossover trial.[18] The efficacy of time-released oxycodone has also been studied in DPN in a multicenter 6-week study of 159 patients.[19] Oxycodone CR was effective in treatment of neuropathy as measured by overall average daily **pain** intensity and rating in subject diaries on a numeric rating scale.

Although few studies have been published reviewing the efficacy of methadone in the treatment of persistent

neuropathic pain, the author's clinical experience has been favorable. An understanding of the pathophysiology of **neuropathic pain** and the ability of methadone to antagonize the NMDA receptor site are clinically demonstrated in **pain** relief reported by patients. In patients on high doses of morphine (>300 mg daily) who remain unresponsive to this treatment, conversion to methadone is an option. Careful titration and respect for the long and variable half-life of this compound is essential. The elderly patient with **neuropathic pain** may respond to very low doses, such as 5 mg daily at bedtime.

The reluctance to use opioids in chronic **pain** patients is in part related to the fear of the potential for abuse. Clinicians should be educated as to the low potential for abuse of opioids in patients who have no history of substance abuse, and in patients who have a positive history for abuse the use of agreements and ongoing rehabilitation counseling are useful. Adverse effects include constipation and cognitive and psychomotor impairment. It is recommended that medication be taken on a regular schedule with additional doses ordered for breakthrough **pain**. Agents should be slowly titrated to the effective dose, and the patient should be prescribed a prophylactic stool softener with a mild laxative to avoid constipation during chronic opioid therapy.

The last of the agents recommended as first-line treatment for **neuropathic pain** is off-label use of tramadol. This agent was evaluated in a multicenter study in patients with diabetic neuropathy. The average daily dose required for **pain** relief in this study of 131 patients was 210 mg.[20] The daily effective dose ranged between 100 and 400 mg. When using this weak mu opioid receptor agonist, which is an inhibitor of norepinephrine and serotonin reuptake, consideration must be given to its potential for abuse and side effects such as dizziness, headache, somnolence, anxiety, nausea, and constipation. Precipitation of seizures is a concern at higher doses. Potential drug interactions with drugs having similar affinity for receptor sites, such as monoamine oxidase inhibitors, TCAs, and selective serotonin reuptake inhibitors should be kept in mind.

Considered second-line treatments, anticonvulsant agents are frequently used in combination with a first-line treatment option. These agents are not FDA-approved for the treatment of **neuropathic pain** with the exception of carbamazepine for trigeminal neuralgia. Trials have been published on lamotrigine use in diabetic neuropathy, HIV-associated neuropathy, trigeminal neuralgia, and central poststroke **pain**. A trial involving 92 patients with HIV-associated neuropathy showed that lamotrigine was more effective than placebo in relieving **pain**. The dose given was 400 to 600 mg in divided doses twice daily.[21] Lamotrigine, however, does not appear to be useful in the treatment of **neuropathic pain** as a result of central poststroke **pain**. Adverse effects commonly included dizziness, unsteadiness, drowsiness, and rash. Rash is a significant concern if the starting dose is too high or the titration too fast. Overall, results remain inconclusive as to lamotrigine's efficacy in the treatment of **neuropathic pain**.[22] Carroll and colleagues reviewed case reports and studies on the role of topiramate in the treatment of DPN.[23] The drug is usually well tolerated with slow dose titration initiated at low doses. Difficulty with concentration, speech hesitancy or word finding difficulties, somnolence, and fatigue are the most commonly reported adverse effects. Researchers found 400 mg daily to be an effective dose, with effective dose ranging from a minimum of 50 mg/day to a maximum effective dose of 600 mg/day. It may be necessary to assess effectiveness over a period of 3 to 12 weeks, and weight loss can be troublesome. The drug, as with lamotrigine, does not appear to be useful in poststroke **pain**. A wide variety of anticonvulsants are used to treat **neuropathic pain** without large, double-blind, placebo-controlled, randomized trial evidence to support their use. These include oxcarbazepine, zonisamide, valproate, tiagabine, and levetiracetam. Published trials are needed to provide evidence-based support for their use in the treatment of **neuropathic pain**.

Other Treatments

The patient suffering from **neuropathic pain** may have impaired functioning contributing to declining social function, isolation, and a diminished quality of life. To address these issues, nonpharmacologic strategies can be recommended, such as physical/ occupational therapy and rehabilitation, group support therapy with other patients with chronic **pain**, cognitive behavioral therapy, interventional therapies, and intrathecal analgesic drug delivery. The pharmacist can assist the patient in accessing the health care system for physical therapy to help with neuromuscular rehabilitation and a possible transcutaneous electrical nerve stimulation (TENS) trial. The

occupational therapist is helpful in transitioning an individual from a loss of function to functional, possibly employable, status. Cognitive behavioral therapy consists of meditation, relaxation, and attention-diversion techniques. Assisting the patient to normalize sleep routines emphasizes sleep hygiene methods and limiting caffeine consumption. In addition, the patient can develop an exercise routine with the help of the multidisciplinary **pain** team members. Finally, interventional treatments can be suggested for those who are unresponsive to other approaches. Examples of interventional treatments are sympathetic nerve blocks, implantable technologies, or chemical/ physical neurolysis. Local anesthetics and corticoid nerve blocks may be used to afford the patient some function while other strategies are being identified. Nerve blocks are temporary, and efficacy is controversial as few placebo-controlled trials have been conducted.[24] Finally, intrathecal drug delivery can be considered. Intrathecal pharmacotherapy is delivered using opioids, clonidine, baclofen, or local anesthetics for those patients who have intractable **pain** and require longterm treatment. Individuals who suffer unmanageable adverse effects from other treatments yet require chronic therapy and have responded positively to a trial are candidates for intrathecal drug delivery.

New and Emerging Treatments

Duloxetine has received FDA approval for treatment of depression and subsequently for DPN. The drug is a serotonin and norepinephrine reuptake inhibitor similar to venlafaxine. Two 12-week trials evaluated the efficacy of duloxetine in DPN.[25,26] The average age of the participants was 60 years, mean duration of diabetes was 11 years, and duration of DPN was 4 years. In total, between the 2 trials, nearly 800 individuals participated. Duloxetine significantly reduced **pain** compared with placebo at doses of 60 mg QD or BID. The higher dose was not found to be superior to the daily dose, however. Potential adverse effects, in order of prevalence, included nausea, dry mouth, constipation, insomnia, dizziness, and somnolence. Duloxetine is metabolized through the cytochrome P-450 1A2 and 2D6 enzyme systems, requiring the pharmacist to review for potential drug interactions with enzyme inhibitors such as ciprofloxacin, cimetidine, or paroxetine. Duloxetine is itself an inhibitor of the 2D6 enzyme system, and this may affect metabolism of TCAs, phenothiazines, and propafenone. Clinically significant adverse drug interactions as yet have not been reported. It is recommended that the drug not be given to patients with renal impairment, specifically those with creatinine clearance <30 mL/min.

Pregabalin has received FDA approval for **neuropathic pain** associated with DPN and PHN. It is pharmacologically similar to gabapentin but has a faster onset of action and shorter titration period. Although the mechanism of action is not completely understood, the target site is the calcium channel. Researchers have completed three 12-week trials for each indication.[27-29] Positive response to the drug was observed within the first week of treatment. In one of the studies, it was reported that the drug was well tolerated with early improvement.[28] Clinically important improvement was defined as >50% reduction in **pain** score as compared with baseline equivalent or a reduction of 3 points on the NRS. Response was not always significant with the 150-mg strength. The 600-mg dose, given in 2 or 3 divided doses, produced a more significant **pain** improvement.

Pregabalin is 2.4 times more potent than gabapentin and has an improved side-effect profile. Differences in bioavailability allow for a shorter titration schedule to effective dose. Safety was shown in studies involving more than 9000 patients with the most common side effects reported as dizziness, somnolence, dry mouth, peripheral edema, blurred vision, and weight gain. The drug will be marketed in late 2005. The Drug Enforcement Adminstration (DEA) has reviewed the drug and has classified pregabalin as a C-V drug. Clinical experience will be needed to evaluate its place in therapy.

NMDA receptors play a key role in the sensitization of central **pain** pathways in **neuropathic pain**. Antagonists at this receptor have been developed and tested, but most of the compounds display poor side-effect profiles. Memantine shows promise as an analgesic in animal models of **pain**. A clinical program sponsored by the manufacturer is under way to study the use of memantine in **neuropathic pain**.

Ziconotide, derived from the venom of a marine snail, can be administered intrathecally as an analgesic for severe

chronic **pain** in those who are intolerant or refractory to other treatments. The drug is approved for use only in appropriate programmable microinfusion pumps either implanted or worn externally for short-term treatment. The mechanism of action is theorized to be a calcium-channel blocker at the primary afferent nerve terminal in the dorsal horn. Use will be specialized, due to its complex method of administration. Side effects such as nystagmus, ataxia, sedation, and hallucinations may further limit its use.[30] Capsaicin transdermal patch is being developed for treatment of **neuropathic pain**. The patch is applied daily for 1 hour to achieve sustained **pain** relief. Phase 2 trials are ongoing for PHN and diabetic neuropathy.[30] GW-1000 (Sativex) is a cannabis extract containing delta-9-tetrahydrocannabinol similar to dronabinol and marijuana. GW-1000 has been approved in Canada for management of **neuropathic pain** associated with multiple sclerosis. It is administered as an oral spray for use under the tongue or inside the cheek. In the United States, GW-1000 is considered a Schedule I drug by the DEA, so importation is currently illegal.[31]

Medication Therapy Management for Persistent Neuropathic Pain

The pharmacist can play a significant and meaningful role in the management of patients with **pain** and especially the complex patient presenting with persistent **neuropathic pain**. The core elements for medication therapy management (MTM) service[32] can be applied to the patient suffering from **pain**.

1. Performing or obtaining necessary assessments of the patient's health status: The pharmacist should assess for **pain** as the fifth vital sign and specifically by using instruments such as the NPS. Pharmacists can conduct foot inspection and filament testing in the diabetic patient. Patients may have difficulty describing **neuropathic pain**; therefore it is important to provide specific adjectives describing **neuropathic pain** in your **pain** quality assessment. Assess the impact **pain** has on daily function and quality of life.

2. Formulating a medication treatment plan, including counseling the patient on expectations regarding medication therapy: The treatment plan should provide an explanation of appropriate goal setting. The patient should understand that **pain** that is long-standing may not respond completely to treatments. Patients need to set goals where they can manage residual **pain**. The treatment plan, with provider approval, should include a moderate exercise program. Support should be solicited from family and friends to prevent social decline and isolation.

3. Monitoring and evaluating patient response to therapy, including safety and effectiveness: Monitoring, especially in the first few days of dosage changes or initiation of new agents, is crucial to the titration process in treating **pain**. The pharmacist should closely follow patients in order to achieve optimum benefits from the regimen prescribed while minimizing and addressing adverse events or other complications as they arise.

*4. Performing a comprehensive medication review to identify, resolve, and prevent medication-related problems, including adverse events related to other medications in addition to the **pain** management regimen and how these interrelate:* The individual suffering from **neuropathic pain** is frequently treated with rational polypharmacy designed to treat the **pain** and other associated symptoms such as anxiety, depression, and spasm. A prospective drug regimen review by the pharmacist on the patient's first visit is essential to optimizing treatment.

5. Documenting the care delivered and communicating information to other care providers: The patient may have multiple providers, including the physician, physical therapist, psychologist, and others involved in the treatment of the chronic **pain**. The pharmacist is often a hub of information for these members of the health care team, and he or she should act as a central communicator.

6. Educating the patient on the understanding and appropriate use of medications: Medications used in the treatment of **neuropathic pain** frequently are prescribed off-label, and patient information sheets are not useful in this setting. Anticonvulsant drugs, some of the opioids, and TCAs are all used off-label for the treatment of **neuropathic pain**. The pharmacist should take extra time to explain these offlabel medications to the patients.

7. Providing information, support, and resources to enhance patient adherence: The patient with **neuropathic pain** is frequently using a complex regimen of medications not only for the treatment of **pain** but also for the treatment of other comorbidities. Nonadherence is a risk in such patients. Pharmacists are specialists in counseling patients on medication use and adherence and can improve patient adherence through appropriate counseling.

8. Coordinating and integrating MTM services within the broader health care management services brought to the patient: The pharmacist can educate patients and families in general about nerve **pain**, explain its pathophysiology in simple terms, provide education on the wide variety of treatment options, and refer the patient to other members of the multidisciplinary team as necessary.

Counseling Points for the Patient with Neuropathic Pain

- A combination of treatment strategies is essential to achieve some degree of relief from chronic **pain** because the **pain** is the result of multiple causes.
- Understand medications, dosing schedules, side effects. You may have to keep track of multiple medications.
- Realize that medications may not be FDA-approved for treatment of **neuropathic pain**, and reference information may not be readily available.
- Be cautious about using alternative or natural medicines to provide relief. These usually are not effective and can be expensive.
- Physical therapy, exercise, and psychological treatments are important to the treatment plan. Keep appointments and be patient with expectations.
- Set reasonable goals for **pain** relief. **Pain** most likely will not be able to be completely cured.
- Understand **neuropathic pain**. Being knowledgeable about your condition gives you an opportunity to have input into the treatment plan.
- Become proactive about your health, and achieve your own successes.

Resources for Pharmacists and Patients

www.theacpa.org The American Chronic **Pain** Association (ACPA) is raising awareness about **neuropathic pain**. Pharmacists can facilitate this initiative by identifying patients with **neuropathic pain** and educating patients and families. A survey sponsored by the ACPA found that **neuropathic pain** is not well understood by the public.[33] The survey was a random sampling of 939 Americans not employed in the medical field. Nearly 34% of the respondents to the telephone survey knew someone with or had the **pain** described as tingling, pins and needles, burning, or electric shocklike sensations. Only 6% recognized these symptoms as nerve **pain**. Educating patients can empower them to manage their own **pain**. The Web site offers support resources such as group support by geographical region.

www.medsch.wisc.edu/painpolicy The University of Wisconsin Web site offers information about **pain** relief and public policy. The aim is to raise awareness about **pain** and to ensure adequate availability of **pain** medications for patient care while minimizing diversion and abuse. The **Pain** and Policy Studies Group (PPSG) facilitates this mission.

www.pharmacy.duq.edu/divPharmPrac.html Duquesne University Mylan School of Pharmacy has established an interdisciplinary chronic **pain** team. The Chronic **Pain** Initiative utilizes the resources of the university to improve the quality of life of those with **pain** and their family members through an interdisciplinary effort focusing on healing of mind, body, and spirit. The team believes that there is much work to be done in educating not only patients and families, but also health care professionals about **pain** management. The Chronic **Pain** Initiative involves students early on in their training as members of the interdisciplinary team model of care. Team members provide support and informational resources for patients, families, and caregivers of those suffering from **pain** to reintroduce hope into their lives.

www.ampainsoc.org The American **Pain** Society (APS) is a multidisciplinary organization composed of professionals who are involved in basic research, clinical research, treatment, advocacy, and public policy regarding **pain**. Resources on the Web site include publications, calendar of events, news, and links to related Web sites.

www.ittakesnerve.org A consumer Web site for the patients and their families who cope with the suffering from **neuropathic pain**. Information includes how to enjoy life and improve the quality of life despite nerve **pain**. The site is associated with the American Chronic **Pain** Association (ACPA).

Conclusion

Neuropathic pain is a chronic disorder associated with much personal suffering, compromised quality of life, and loss of function. The patient is optimally treated by a multidisciplinary team of health care professionals using a combination of therapies such as rational polypharmacy, physical and occupational therapy, and cognitive therapies. The pharmacist plays an integral role on the team treating the patient with **neuropathic pain** through application of medication management principles in the community or hospital practice setting. These medication management principles can optimize therapeutic outcomes for individual patients.

For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. A. Stahl, Pharmacy Times, 241 Forsgate Drive, Jamesburg, NJ 08831; or send an e-mail request to: astahl@ascendmedia.com .

Hildegarde J. Berdine, BS, PharmD, BCPS is Assistant Professor of Pharmacy Practice, Duquesne University Mylan School of Pharmacy

Back to Top

arthritis Also found in: Medical, Columbia, Wikipedia, Hutchinson 0.03 sec.

ar·thri·tis (är-thrī'tĭs)
n.

Inflammation of a joint, usually accompanied by pain, swelling, and stiffness, and resulting from infection, trauma, degenerative changes, metabolic disturbances, or other causes. It occurs in various forms, such as bacterial **arthritis**, osteoarthritis, or rheumatoid **arthritis**.

ar·thrit'ic (-thrĭt'ĭk) *adj. & n.*

ar·thrit'i·cal·ly *adv.*

Thesaurus

Legend: | Synonyms | Related Words | Antonyms

Noun 1.

arthritis - inflammation of a joint or joints

| inflammatory disease - a disease characterized by inflammation

| atrophic **arthritis**, rheumatoid **arthritis**, rheumatism - a chronic autoimmune disease with inflammation of the joints and marked deformities; something (possibly a virus) triggers an attack on the synovium by the immune system, which releases cytokines that stimulate an inflammatory reaction that can lead to the destruction of all components of the joint

| degenerative **arthritis**, degenerative joint disease, osteoarthritis - chronic breakdown of cartilage in the joints; the most common form of **arthritis** occurring usually after middle age

| gout, gouty **arthritis**, urarthritis - a painful inflammation of the big toe and foot caused by defects in uric acid

metabolism resulting in deposits of the acid and its salts in the blood and joints
spondylarthritis - **arthritis** that affects one or more of the intervertebral joints in the spine

Mentioned in

amyloidosis
anti-inflammatory
anti-inflammatory
drug
anti-TNF compound
Arava
atrophic **arthritis**
chrysotherapy
Enbrel
etanercept
infliximab
leflunomide
nonsteroidal anti-inflammatory
nonsteroidal anti-inflammatory
drug
NSAID
osteoarthritis
propanoic acid
propionic acid
Remicade
rheumatoid factor
More results

References in classic literature

No references found

Dictionary/thesaurus browser

artfully
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Full browser

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Arthritis and Rheumatism International
arthritis deformans
Arthritis Foundation
Arthritis in children
Arthritis in children
Arthritis in children
Arthritis in children
arthritis mutilans
Arthritis National Research Foundation (Long Beach, CA)
Arthritis Prevention and Education Program
Arthritis Research Campaign
Arthritis Research Campaign
Arthritis Research Centre of Canada
Arthritis Research Centre of Canada (Vancouver, Canada)
Arthritis Self-Management Program
Arthritis, Juvenile
Arthritis-Specific Health Index
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NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	DEC 21	IPC search and display fields enhanced in CA/CAplus with the IPC reform
NEWS	4	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS	5	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS	6	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS	7	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS	8	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS	9	JAN 30	Saved answer limit increased
NEWS	10	JAN 31	Monthly current-awareness alert (SDI) frequency added to TULSA
NEWS	11	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS	12	FEB 22	Status of current WO (PCT) information on STN
NEWS	13	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS	14	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS	15	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS	16	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS	17	FEB 28	TOXCENTER reloaded with enhancements
NEWS	18	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental spectral property data
NEWS	19	MAR 01	INSPEC reloaded and enhanced
NEWS	20	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS	21	MAR 08	X.25 communication option no longer available after June 2006

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
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* available and contains the CA role and document type information. *
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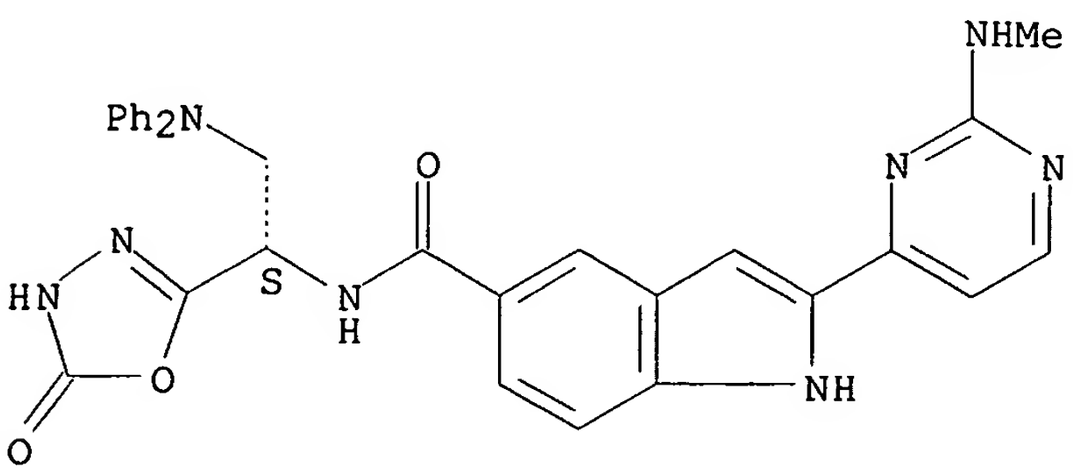
=> s 669713-30-8/rn
L1 1 669713-30-8/RN

=> d

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN **669713-30-8** REGISTRY
ED Entered STN: 01 Apr 2004
CN 1H-Indole-5-carboxamide, N-[(1S)-1-(4,5-dihydro-5-oxo-1,3,4-oxadiazol-2-yl)-2-(diphenylamino)ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H26 N8 O3
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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L2 5 669713-30-8/RN

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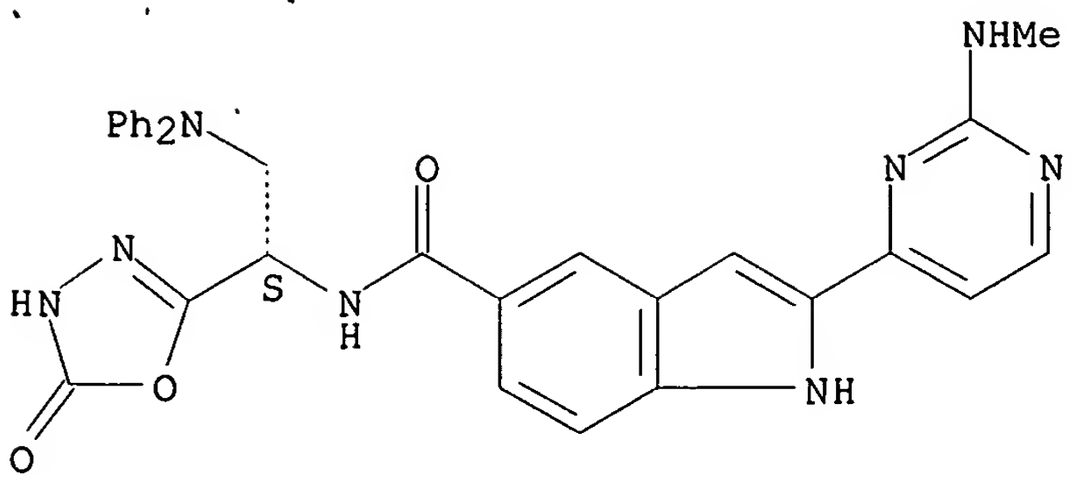
L2 ANSWER 1 OF 5 CAPLUS
ACCESSION NUMBER: 2006:148987 CAPLUS
DOCUMENT NUMBER: 144:226260
TITLE: Use of TRAIL and IκB kinase inhibitors in cancer treatment
INVENTOR(S): Loehn, Matthias; Ivashchenko, Yuri
PATENT ASSIGNEE(S): Sanofi-Aventis Deutschland G.m.b.H., Germany
SOURCE: Ger. Offen., 26 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 102004034380	A1	20060216	DE 2004-102004034380	20040716
PRIORITY APPLN. INFO.:			DE 2004-102004034380	20040716

AB The use of indole- or benzimidazole-based IκB kinase inhibitors in combination with TRAIL (tumor necrosis factor ligand) to treat cancer is disclosed. Thus, induction of apoptosis in cultures of THP1 and U937 cells by TRAIL and a pyrimidinylindolecarboxamide or pyrimidinylbenzimidazolecarboxamide IκB kinase inhibitor (**669713-30-8** and 669713-32-0, resp.) was synergistic.
IT **669713-30-8**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of TRAIL and IκB kinase inhibitors in cancer treatment)
RN 669713-30-8 CAPLUS
CN 1H-Indole-5-carboxamide, N-[(1S)-1-(4,5-dihydro-5-oxo-1,3,4-oxadiazol-2-yl)-2-(diphenylamino)ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L2 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:220328 CAPLUS
DOCUMENT NUMBER: 140:270869
TITLE: Preparation of pyrimidinylindolecarboxamides and pyrimidinylbenzimidazolecarboxamides as inhibitors of IκB kinase.
INVENTOR(S): Ritzeler, Olaf; Jaehne, Gerhard
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004022553	A1	20040318	WO 2003-EP8629		20030805
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
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CA 2498559	AA	20040318	CA 2003-2498559		20030805
AU 2003263196	A1	20040329	AU 2003-263196		20030805
EP 1530568	A1	20050518	EP 2003-793685		20030805
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
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JP 2005539054	T2	20051222	JP 2004-533319		20030805
US 2005197353	A1	20050908	US 2003-642970		20030818
NO 2005001337	A	20050503	NO 2005-1337		20050315
PRIORITY APPLN. INFO.:			DE 2002-10237722	A	20020817
			US 2002-434749P	P	20021219
			WO 2003-EP8629	W	20030805

OTHER SOURCE(S): MARPAT 140:270869
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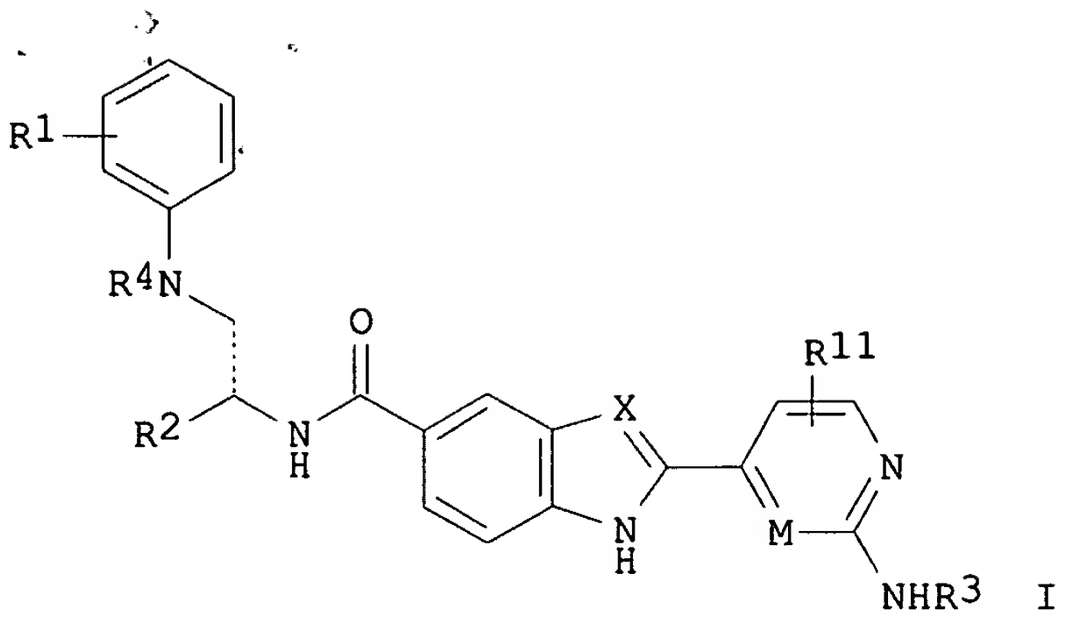


I

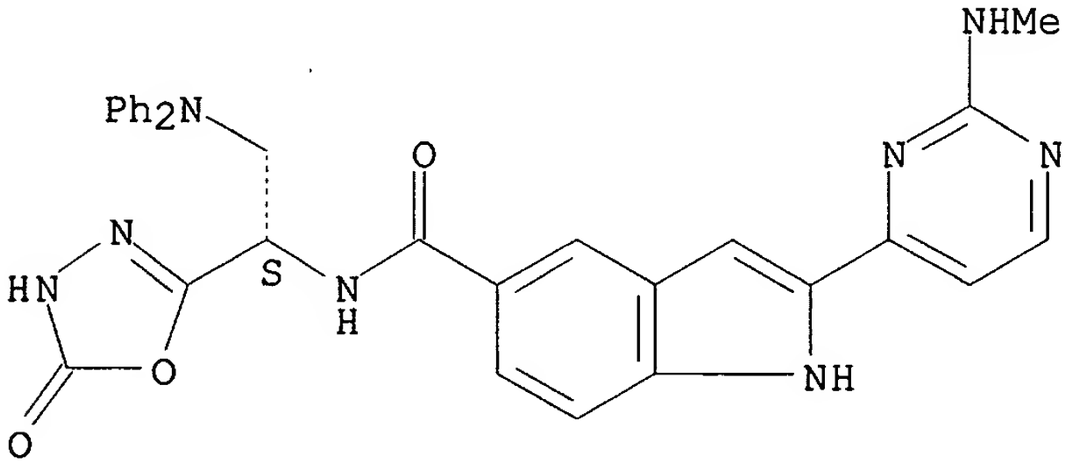
AB Title compds. [I; X, M = N, CH; R1, R11 = H, F, Cl, Br, iodo, alkyl, cyano, CF3, OR5, NR5R6, COR5, SOxR5, etc.; x = 0-2; R3, R5, R6 = H, alkyl; R2 = (substituted) imidazolyl, imidazolidinyl, indazolyl, isothiazolyl, isoxazolyl, morpholinyl, piperazinyl, pyrazolyl, tetrazolyl, thiadiazolyl, thiazolyl, thiomorpholinyl, triazolyl, etc.; R4 = (substituted) (fused) pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, phthalazinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, etc.], were prepared Thus, 2-(2-methylaminopyrimidin-4-yl)-1H-indole-5-carboxylic acid [(S)-2-diphenylamino-1-hydrazinocarbonylethyl]amide (preparation given) in CH2Cl2 was treated with phosgene followed by stirring for 15 h to give 76% 2-(2-methylaminopyrimidin-4-yl)-1H-indole-5-carboxylic acid [(S)-2-diphenylamino-1-(5-oxo-4,5-dihydro[1,3,4]-oxadiazol-2-yl)ethyl]amide. The latter inhibited IκB kinase with IC50 = 0.050 μM.

IT **669713-30-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrimidinylindolecarboxamides and pyrimidinylbenzimidazolecarboxamides as inhibitors of IκB kinase)

RN 669713-30-8 CAPLUS

CN 1H-Indole-5-carboxamide, N-[(1S)-1-(4,5-dihydro-5-oxo-1,3,4-oxadiazol-2-yl)-2-(diphenylamino)ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:220204 CAPLUS
DOCUMENT NUMBER: 140:247090
TITLE: Use of substituted indole and benzimidazole IκB kinase inhibitors for the treatment of pain
INVENTOR(S): Michaelis, Martin; Ritzeler, Olaf; Jaehne, Gerhard; Rudolphi, Karl; Geisslinger, Gerd; Schaible, Hans-Georg
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany

SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004022057	A1	20040318	WO 2003-EP8628	20030805
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
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AU 2003271555	A1	20040329	AU 2003-271555	20030805
EP 1531819	A1	20050525	EP 2003-753349	20030805
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003013555	A	20050712	BR 2003-13555	20030805
CN 1674899	A	20050928	CN 2003-819542	20030805
JP 2005539053	T2	20051222	JP 2004-533318	20030805
US 2004116494	A1	20040617	US 2003-642974	20030818
NO 2005001339	A	20050503	NO 2005-1339	20050315

PRIORITY APPLN. INFO.:		
DE 2002-10237723	A	20020817
US 2002-434628P	P	20021219
WO 2003-EP8628	W	20030805

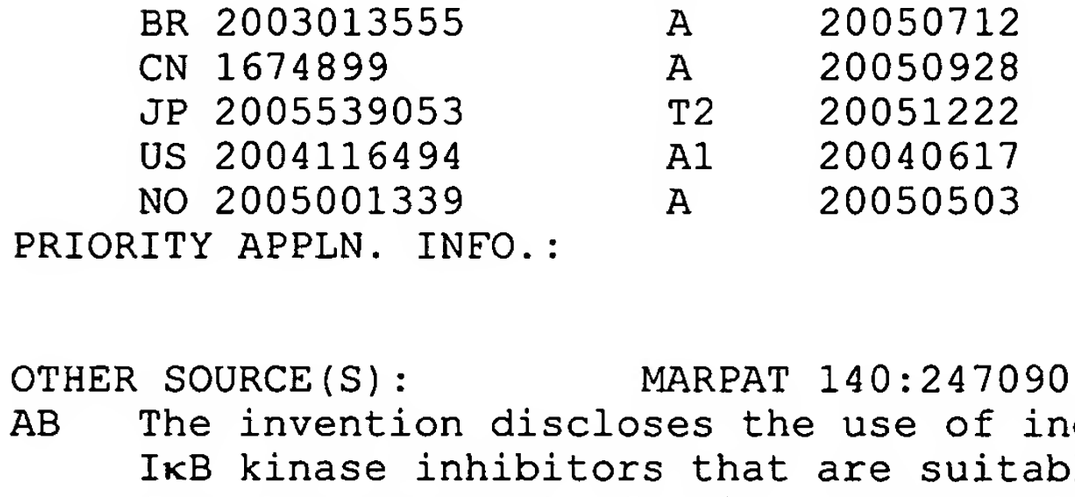
OTHER SOURCE(S): MARPAT 140:247090

AB The invention discloses the use of indole derivative and benzimidazole derivative IκB kinase inhibitors that are suitable for producing medicaments for the treatment of pain. Preparation of compds. is described.

IT **669713-30-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(indole derivative and benzimidazole derivative IκB kinase inhibitors for the treatment of pain)

RN 669713-30-8 CAPLUS
CN 1H-Indole-5-carboxamide, N-[(1S)-1-(4,5-dihydro-5-oxo-1,3,4-oxadiazol-2-yl)-2-(diphenylamino)ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2005:227501 USPATFULL

TITLE: Indole derivatives or benzimidazole derivatives for modulating IkB kinase
INVENTOR(S): Ritzeler, Olaf, Bad Soden, GERMANY, FEDERAL REPUBLIC OF
Jaehne, Gerhard, Frankfurt, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S): AVENTIS PHARMA DEUTSCHLAND GMBH, Frankfurt am Main, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

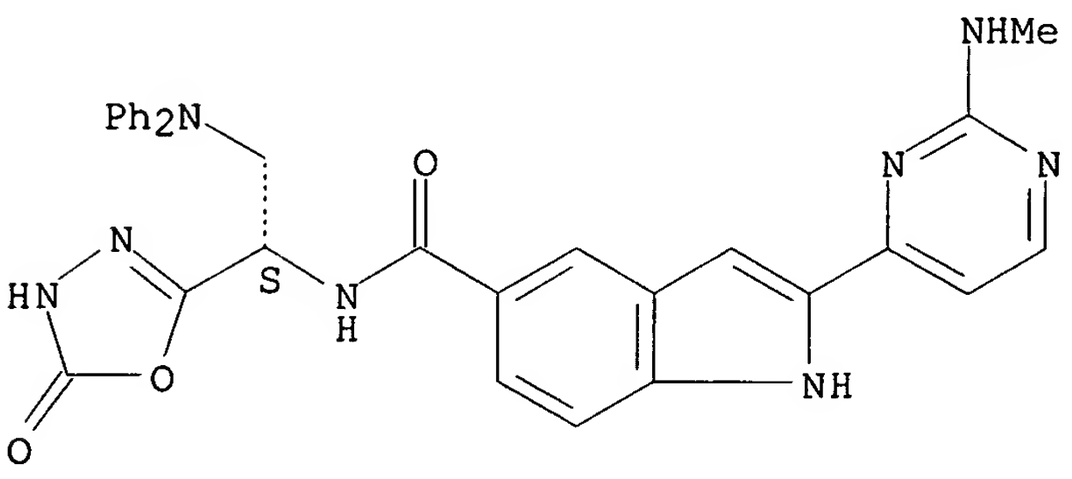
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2005197353	A1	20050908	
APPLICATION INFO.:	US 2003-642970	A1	20030818	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	DE 2002-10237722	20020817	
	US 2002-434749P	20021219	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Julie Anne Knight, Aventis Pharmaceuticals, Inc., Patent Department, Route #202-206/ P.O. Box 6800, Bridgewater, NJ, 08807-0800, US
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 1597
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to indole derivatives or benzimidazole derivatives, to processes for preparing such compounds, to pharmaceutical compositions comprising such compounds, and methods for the prophylaxis and therapy of a disease associated with an increased activity of IκB kinase comprising administering such compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **669713-30-8P**
(preparation of pyrimidinylindolecarboxamides and pyrimidinylbenzimidazolecarboxamides as inhibitors of IκB kinase)
RN 669713-30-8 USPATFULL
CN 1H-Indole-5-carboxamide, N-[(1S)-1-(4,5-dihydro-5-oxo-1,3,4-oxadiazol-2-yl)-2-(diphenylamino)ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L2 ANSWER 5 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2004:152272 USPATFULL
TITLE: Use of IkappaB-kinase inhibitors in pain therapy
INVENTOR(S): Michaelis, Martin, Frankfurt, GERMANY, FEDERAL REPUBLIC OF
Ritzeler, Olaf, Bad Soden, GERMANY, FEDERAL REPUBLIC OF
Jaehne, Gerhard, Frankfurt, GERMANY, FEDERAL REPUBLIC OF
Rudolphi, Karl, Mainz, GERMANY, FEDERAL REPUBLIC OF
Geisslinger, Gerd, Bad Soden, GERMANY, FEDERAL REPUBLIC OF
Schaible, Hans-Georg, Jena, GERMANY, FEDERAL REPUBLIC

OF
PATENT ASSIGNEE(S): AVENTIS PHARMA DEUTSCHLAND GMBH, Frankfurt am Main, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

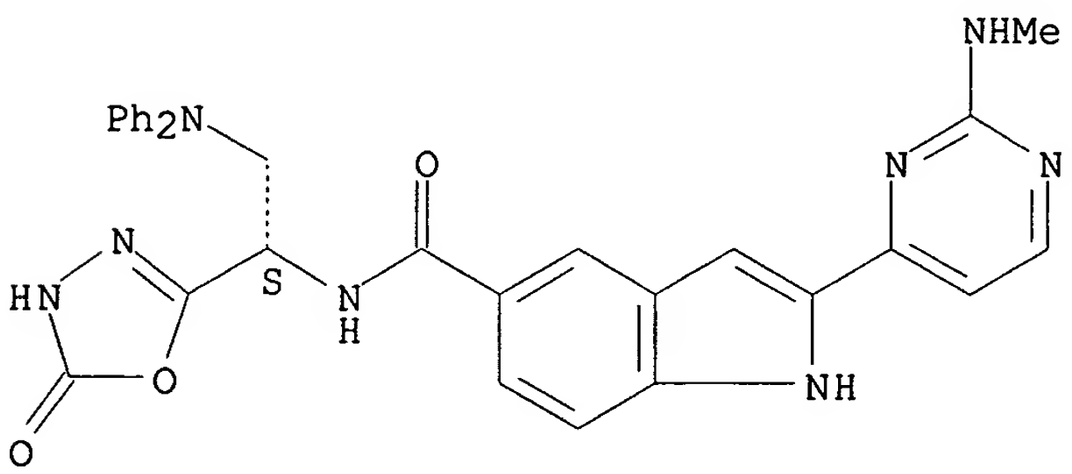
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004116494	A1	20040617	
APPLICATION INFO.:	US 2003-642974	A1	20030818	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	DE 2002-10237723	20020817	
	US 2002-434628P	20021219	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ROSS J. OEHLER, AVENTIS PHARMACEUTICALS INC., ROUTE 202-206, MAIL CODE: D303A, BRIDGEWATER, NJ, 08807
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 2761
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the use of IκB-kinase Inhibitors and methods for the prophylaxis and therapy for treating pain comprising administering such compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **669713-30-8P**
(indole derivative and benzimidazole derivative IκB kinase inhibitors for the treatment of pain)
RN 669713-30-8 USPATFULL
CN 1H-Indole-5-carboxamide, N-[(1S)-1-(4,5-dihydro-5-oxo-1,3,4-oxadiazol-2-yl)-2-(diphenylamino)ethyl]-2-[2-(methylamino)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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FILE 'REGISTRY' ENTERED AT 00:03:08 ON 18 MAR 2006
L1 1 S 669713-30-8/RN

FILE 'CAPLUS, USPATFULL' ENTERED AT 00:03:36 ON 18 MAR 2006
L2 5 S 669713-30-8/RN